

* NOTICES *

JPO and NCIP are not responsible for any damages caused by the use of this translation.

1. This document has been translated by computer. So the translation may not reflect the original precisely.
2. **** shows the word which can not be translated.
3. In the drawings, any words are not translated.

DETAILED DESCRIPTION

[Detailed Description of the Invention]

Buffer system for stabilizing remedy pharmaceutical preparation This invention describes the complexing buffer system for raising the stability of remedy pharmaceutical preparation during the period of manufacture and preservation. Since it has a special property, the buffer mixture by invention is suitable for especially application out of intestines. It has the fitness for manufacturing a contrast-medium solution above all. The technical actual condition Although the buffer solution of water-solution pharmaceutical preparation is often used in the business on pharmaceutical sciences, in order to save at stability, a certain fixed pH value is required. Since there is optimal pH value different, respectively also in a decomposition process, for example, hydrolysis, or oxidation, and solubility, with injection and the water solution for infusion solutions, it is the physiological pH value 7.4 to ophthalmology medicine and a list. Many efforts are made so that it may bring close most (= normal hydrogen ion concentration). Since the buffer capacity of plasma is large, at least when buffer capacity is a low solution for injection (volume ≤ 20 ml), even if the variation rate from a ** pH point (= 7.4) migrates to the quite big pH range 4-9, it is accepted (Physikalische Pharmazie, Ed.:H.Stricker, Wissenschaftliche Verlagsgesellschaft mbH Stuttgart, 3 Aufl., 1987). A table 1 lists the buffer system of the utilization intestines outside used commonly pharmacologically (Pharmazeutische Technologie, Eds.:H.Sucker, P.Fuchs und P.Speiser, Georg Thieme Verlag Stuttgart, 1978).

Table 1: Buffer system commonly used by utilization intestines outside

物質 1	物質 2	p H 範囲	最大緩衝能 を示す p H
酢酸ナトリウム	酢酸	3.8 ~ 5.6	4.7
リン酸二水素 ナトリウム	リン酸水素 二ナトリウム	5 ~ 8	6.8
グリシン	水酸化ナトリウム	8.6 ~ 12.8	11.2
クエン酸	リン酸 二ナトリウム	2.2 ~ 7.8	約 5
トロメタモール	塩酸	7.2 ~ 9.0	約 8

The important remedy group of utilization intestines outside has an X-ray contrast medium containing iodine, and many are used as a solution for infusion solutions. here -- as a buffer substance -- a table 1 -- fatty tuna -- although a meta-mall [tris (hydroxymethyl) aminomethane, 2-amino-2-(hydroxymethyl)-1, and 3-propanediol] (for example, contained in ultra Bisto (trademark), Omnipaque (trademark), or the salt last (trademark)) and a sodium dihydrogenphosphate (for example, contained in Conray (trademark)) are mentioned, a sodium hydrogencarbonate (for example, contained in Isovist (trademark)) is also used.

pH range 7.2-9.0 set, and buffer action is good and extensive possibility is acquired by accommodation of pH [it] point -- being based -- fatty tuna -- the meta-mall buffer solution (= tris) has obtained special positioning here. if it compares with the phosphate buffer by which a rear-spring-supporter activity is carried out in the range of pH 5-8 -- in addition, fatty tuna -- there is no description which is making an issue of possibility of

building the ion from a glass primary container and precipitation about the meta-mall buffer solution.

German patent DE 2926850 Although the manufacture or the sterilization approach containing iodine of a special contrast-medium solution is in the range to indicate, this is based on the pH value of the amine buffer solution falling depending on temperature. fatty tuna -- the pH value of the meta-mall buffer solution or the meglumine buffer solution (pH 7.0-7.6) -- between sterilization 3.5-5.5 up to -- generation of the iodide under manufacture was able to be clearly decreased as a falling result. If it sterilizes succeedingly, the pH value of this solution will return to the value of a starting point mostly again.

If the X-ray contrast medium (RKM) used commonly is saved at a room temperature (15-25 degrees C) and light is intercepted, its many are stable exceeding three years. It becomes impossible for a decomposition process to extend the retention period of a product more than it in many cases. If a destabilization reaction these matter groups are indicated to be occurs, a pH value and a color will change in connection with it, and the content of an active substance will decrease. The content of an iodide and an isolation amine is taken into consideration as an indicator to such chemical decomposition of RKM (Kontrastmittel, Ed.:U.Speck, Springer-Verlag Berlin, 3.Aufl., 1991).

Therefore, the technical problem of this invention presents an activity with the new buffer system which has good buffer action in the physiology range, and when saving and manufacturing pharmaceutical-sciences dispensing, it is to decrease a medicinal decomposition reaction especially in the case of heat sterilization. This technical problem is solved by the buffer system by invention so that it may characterize to a claim. The buffer water-solution system by this invention is involved in the mixture which consists of the aliphatic series which has the amine which has physiological compatibility, and physiological compatibility, or an aromatic series organic acid.

It is interpreted as the amine or the acid with physiological compatibility being the matter which is already permitted as an additive for a remedy or remedies, or exists in the organism of Homo sapiens or an animal under physiology conditions in inside.

All the amines that show physiological compatibility are taken into consideration as an amine component of the buffer-solution mixture by this invention. N-methyl glucamine (meglumine) and/or fatty tuna -- a meta-mall (2-amino-2-(hydroxymethyl)-1, 3-propanediol, tris) uses it preferably -- having -- especially -- fatty tuna -- the meta-mall is excellent.

As an acid component of the buffer-solution mixture by this invention The carboxylic acid of monovalence or many ** (for example, a succinic acid, a maleic acid, a benzoic acid), Hydroxycarboxylic acid (for example, a glycolic acid, a citric acid, a malic acid, or a lactic acid), A keto acid (for example, alpha-ketoglutarate) or a sulfonic acid (for example, 2-[4-(2-hydroxyethyl)-1-piperazino]-ethane sulfonic acid (HEPES)), and amino acid (For example, priority is given to a glycine, an aspartic acid, a phenylalanine, a lysine, an arginine, especially natural L-amino acid) Or those salts are used. the case where priority is given especially -- for example, fatty tuna -- a succinic acid is compounded with a meta-mall. The component used in the buffer-solution mixture of invention may be mixed with the mole fraction of arbitration. The mixed molar fraction other than the standard mol mixing molar fraction 1:1 (for example, 10 mM tris and 10 mM glycine) can be extended further, and it can also adjust from 1:99 to 99:1. Mixed molar fraction It reaches 25:75. When it is made 75:25, there are some examples from which a good result is obtained dramatically.

The salt of the principal component of the buffer solution is also used besides the matter commonly used by expert like caustic soda or a hydrochloric acid in order to adjust the pH value of the buffer-solution mixture by this invention.

When the buffer solution of this invention is especially suitable, taking into consideration a requirement physiological about each remedy pharmaceutical preparation in order to show buffer capacity sufficient in the range of pH 4-9, it becomes possible to double with a minimum pH value required for stabilization. the conventional fatty tuna -- the meta-mall buffer solution -- almost -- 7.2-9.0 Although buffer capacity sufficient in just the pH range was shown, the buffer system of this invention can be used for validity to still lower pH range if needed to this depending on the case. in addition -- being also alike -- the buffer system of this invention -- the -- special -- physical and chemical property -- being based -- etc. -- it is proved that the conventional buffer system is excelled also in the range of pH point (abbreviation 7.4). Therefore, by using the buffer solution of this invention, the decomposition process which happens when other conditions are equal is often avoidable. In addition, although it can be managed even if it, for example, does not add selectively a pharmaceutical preparation assistant like a complexing agent (for example, calcium disodium edetate) if the

buffer-solution mixture of invention is used, especially this is because self works as a complex when the buffer-solution mixture of this invention is suitable. In addition, the advantage which the pharmaceutical preparation of invention has also has the damage by the microorganism in not generating the precipitation with the ion from a primary container, either. Furthermore, the outstanding compatibility is notably shown especially in the pharmaceutical preparation of invention.

As for non-***** (injection and solution for infusion solutions) by this invention, a pH value is about adjusted by 4-9, or 5-8. however, the pH value which it aims at in being special -- 6.0-8.0 or -- 5.0-6.7 it is .

The buffer-solution mixture of this invention shows clear temperature dependence about the pH value. It was shown that dip in case the pH value of buffer-solution **** by this invention descends depending on temperature is clearly related to a surprising thing in a starting point pH. although the pH value of the pharmaceutical preparation by this invention descends between heat sterilization (121 degrees C, 20 minutes) in being special -- the value -- a pH unit -- 0.5 or [exceeding] -- or it is 1-3. The drop range of pH which happens during sterilization, and the decomposition reaction generated by the case with it are controllable by choosing the buffer system of invention about a special remedy agent for the object.

In a specific case, consideration of avoiding the special decomposition process which occurs during sterilization desires to lessen pH drop further.

the time of manufacturing the pharmaceutical preparation of this invention -- usual osmole concentration -- 200 - 1200 mOsm/kg -- or -- 200 - 1000 mOsm/kg -- or -- especially -- desirable -- 250 It is set as 850 mOsm/kg in between.

the buffer system of this invention considers as the description -- general -- the total concentration -- low -- carrying out -- the range of 2-40mM -- it is -- however -- desirable -- 10 - 20 mM -- or -- It is in using 5-15mM. The buffer system of this invention is suitable for stabilization of a contrast medium, and stabilization of the X-ray contrast medium based on the aromatic series matter which especially contains iodine with the special method. The stabilization at the time of manufacture demonstrates effectiveness here one, and this can be returned to a part by only pH drop in a sterilization process. fatty tuna -- the meta-mall buffer solution (pH 7.5) -- comparing -- for example, the fatty tuna of invention -- a meta-mall / glycine buffer solution (pH 7.5) was used, and in the iopromido solution (iodine 300 mg/ml), in sterilization (121 degrees C, 20 minutes), 1 time and when it carried out repeatedly, it was proved that generation of an iodide decreases clearly. pH of the temperature dependence which the buffer solution of invention shows at a starting point pH -- fatty tuna -- this data was wonderful, because whether it is small was descending when compared to a meta-mall / HCl buffer solution. the same result -- fatty tuna -- a meta-mall / succinic-acid buffer solution, or fatty tuna -- it was able to obtain using a meta-mall / HEPES buffer solution (pH 7.5).

While maintaining sufficient buffer capacity By having acquired possibility of adjusting less than 7.0 pH value, it is permitted that the buffer system of invention, in addition to this, strengthens the stability at the time of manufacture further. for example, the pH value of an iopromido solution (iodine 300 mg/ml) -- the fatty tuna of this invention -- if it adjusts to pH 6.5 in a meta-mall / succinic-acid buffer solution -- the fatty tuna for a comparison -- compared with the meta-mall buffer solution, the result to which the iodides generated between sterilization (20 minutes, 121 degrees C) decrease in number still more wonderfully was obtained. Since this effectiveness happened notably when sterilization time amount was lengthened further, especially the buffer system of this invention is applicable also to repeat sterilization of an X-ray-contrast-medium solution, when suitable.

the point that the buffer system of this invention is [as opposed to / especially / the buffer solution currently used from the former] excellent -- also taking -- it is in not correcting but raising further the stability of the X-ray-contrast-medium solution at the time of preservation.

If the buffer system of this invention is used, since a decomposition reaction will decrease, duration of service exceeds three years as usually, and it will also mainly reach in four - six years, or five - 10. As a special scale which sees the stability of this solution, the content of iodine, and when special, the content of an isolation amine other than the parameter (for example, a pH value and the color of a solution) known by the expert here is taken into consideration. If it does in this way, the iodine content of an X-ray-contrast-medium solution (concentration: iodine 300 mg/ml) leads the total retention period (duration of service), for example. 75 Less than [mug/ml] and it are also stopped [ml] less than mainly in 50-30microg /.

If the buffer solution of invention is especially used depending on the start pH value of an X-ray-contrast-medium solution in a suitable case, it will result in the result to which the amine generation under preservation

decreases further. the isolation amine which this solution (for example, iodine 300mg/ml) contains -- a usually and activity term period -- under 0.3 % and it -- mainly -- 0.1 -- or -- It is under in 0.05 %.

such especially the X-ray-contrast-medium solution (iopromido) that was manufactured using the buffer solution of this invention in the suitable case when the retention period in March already passed in higher temperature (40 degrees C) -- fatty tuna -- it was proved that iodides are decreasing in number clearly compared with meta-mall buffer solution (starting point pH value = 7.5 and 6.5). Furthermore depending on the starting point pH value, it was checked selectively that the amine content is decreasing only. In addition, the shown surprising results were some cases whose decrements of a complexing agent (calcium disodium edetate) decrease clearly in a contrast-medium testing liquid, when the buffer solution of invention existed. According to this data, if the buffer solution of this invention is used for manufacture of an X-ray-contrast-medium solution, strong possibility that the complexing agent to add is reduced greatly or all are removed will be opened. Especially the buffer solution of this invention is used by the aforementioned property out of intestines, and fits stabilization of the X-ray contrast medium of the hydrophilic property generally known for the radiodiagnosis. When the X-ray contrast medium which belongs to this first is mentioned, once, for example An amidotrizoic acid salt, Metrizoic acid salt, iopromido, N, and N'-screw (2, 3-dihydroxy propyl)-5-hydroxy acetyl amino - 2, 4, 6-triiodo-N-methyl isophthalamide, iothexol, iopamidol, and Io -- SHIMIDO, ioversol, and iomeprol -- IOKUSAGURATO Io -- a pen toll, ioxilan, and Io -- gold [BITORI] -- iotrolan, N, and N'-screw [3-carbamoyl-5-(2, 3-dihydroxy propyl carbamoyl)- 2, 4, and 6-triiodo-phenyl]-N -- an N'-screw (2, 3-dihydroxy propyl)-chestnut amide and Io -- there is JIKUSA Norian and a part of these are used for a computed tomography (CT). At this time, an X-ray contrast medium may be encapsulated by liposome.

In addition, the buffer system of invention is used also for other remedy agent water solutions or suspension (for example, crystal suspension, liposome, a micro particle, a nano particle, a microcapsule, or a nano capsule) regardless of the application approach (for example, the outside of intestines, taking orally, a part (ophthalmology medicine is also included)), when special. When it mentions without limiting the example here, there are for example, a painkiller/antiphlogistic, an antibiotic, a cell proliferation inhibitor, a virus inhibitor, etc. as an active substance for a therapy especially, for example other than MRT contrast media, such as Gd-DTPA, Gd-EOB-DTPA, Gd-DOTA, Gd-BOPTA, Mn-DPDP, and a GADOBU trawl, or an ultrasonic contrast medium. These active substance groups can also show as liposome pharmaceutical preparation. Example on enforcement: Although the following example explains the object of this invention, it does not limit this to an example.

example 1: -- fatty tuna -- stability of the iopromido solution using a meta-mall / HCl buffer solution Iodine concentration 300 mg/ml -- having -- fatty tuna -- the iopromido solution (pH is mostly adjusted to 7.5 or 6.5 by HCl) using the meta-mall (20 mM) buffer solution was manufactured, and only the time amount which mentioned the aliquot of this solution to the table within the closed cylinder for injection of 10 ml carried out autoclave processing (121 degrees C). Thus, about the obtained sample, the trial of pH, an iodide content, and an amine content (aromatic amine of isolation) was performed.

出発点 p H 値	殺菌時間 〔分〕	p H 変化	ヨウ化物 含有量 〔 μ g/ml〕	アミン 含有量 〔重量%〕
7.5	20	- 0.10	8.9	0.019
	60	- 0.12	9.5	0.025
	180	- 0.18	11.9	0.055
6.5	20	- 0.15	8.9	0.010
	60	- 0.18	8.7	0.011
	180	- 0.22	10.2	0.017

Example 2: Iopromido solution using a glycine (10 mM) / tris (10 mM) buffer solution Stability After adjusting

a pH value to (7.5 and 6.5), only the time amount which mentioned to the table two iopromido solutions (iodine 300mg/ml) which used a glycine (10 mM) / tris (10 mM) buffer solution like the example 1 carried out autoclave processing (121 degrees C). About the sample, the trial of pH, an iodide content, and an amine content (aromatic amine of isolation) was performed.

p H 値	殺菌時間 〔分〕	p H 変化	ヨウ化物 含有量 〔 μ g/ml〕	アミン 含有量 〔重量%〕
7.5	20	-0.11	5.1	0.016
	60	-0.13	5.5	0.029
6.5	20	-0.17	6.3	0.010
	60	-0.23	6.5	0.012

Example 3: Iopromido solution using a succinic acid (10 mM) / tris (10 mM) buffer solution Stability This trial was performed like the example 2.

p H 値	殺菌時間 〔分〕	p H 変化	ヨウ化物 含有量 〔 μ g/ml〕	アミン 含有量 〔重量%〕
7.5	20	-0.16	1.8	0.021
	60	-0.22	3.6	0.050
6.5	20	-0.17	0.9	0.021
	60	-0.24	1.9	0.033

Example 4: Iopromido ** using HEPES (10 mM) / tris (10 mM) buffer solution Stability of liquid This trial was performed like the example 2.

p H 値	殺菌時間 〔分〕	p H 変化	ヨウ化物 含有量 〔 μ g/ml〕	アミン 含有量 〔重量%〕
7.5	20	-0.09	2.3	0.020
	60	-0.17	5.4	0.049
6.5	20	-0.06	6.2	0.008
	60	-0.11	6.8	0.013

Example 5: Stability of the iopromido solution using the glycine (20 mM) buffer solution After adjusting a pH value to (abbreviation 7.5 and 6.5), two iopromido solutions (iodine 300mg/ml) which used the glycine (20 mM) buffer solution were processed like the example 1.

出発点 p H 値	殺菌時間 〔分〕	p H 変化	ヨウ化物 含有量 〔 μ g/ml〕	アミン 含有量 〔重量%〕
7.5	20	- 0.24	2.2	0.025
	60	- 0.33	4.0	0.048
	180	- 0.68	7.2	0.092
6.5	20	- 0.38	1.0	0.010
	60	- 0.66	1.4	0.013
	180	- 0.89	2.3	0.021

Example 6: Stability of the iopromido solution using the succinic-acid (20 mM) buffer solution This trial was performed like the example 5.

出発点 p H 値	殺菌時間 〔分〕	p H 変化	ヨウ化物 含有量 〔 μ g/ml〕	アミン 含有量 〔重量%〕
7.5	20	- 0.27	2.9	0.056
	60	- 0.63	7.2	0.145
	180	- 1.07	16.6	0.348
6.5	20	- 0.16	1.4	0.034
	60	- 0.25	4.4	0.092
	180	- 0.40	11.6	0.229

example 7: -- fatty tuna -- temperature dependence of the pH value of the meta-mall buffer solution 20 mM fatty tuna -- a meta-mall solution -- 0.1 N a hydrochloric acid -- using -- pH 7.5 -- adjusting -- the temperature dependence of the pH -- Knick Shrine pH meter 761 was used and it asked by the existence of temperature compensation or temperature compensation. The result is illustrated to drawing 1.

Example 8: Temperature dependence of various buffer-solution pH values Various buffer water solutions (each buffer presentation is set to 10 mM) are manufactured, and it is Knick about the temperature dependence of pH. Shrine pH meter It asked using 761. About the temperature of the buffer solution, it is an outside type sensor each time. Pt-100 It measures, it ****s in it and the temperature of a pH meter is amended. The result is illustrated to drawing 2 and 3.

example 9: -- stability [/ in three months of the iopromido solution by the various buffer solutions] the iopromido solution (iodine 300mg/ml) containing the buffer solution manufactured like examples 1 and 2 -- first -- Within the glass syringe of 10 ml, autoclave processing (20 minutes, 121 degrees C) is carried out, and rear-spring-supporter neglect is succeedingly carried out into an air conditioner in 40 degrees C in three months.

this -- being concurrent -- starting point pH value (before sterilization) 7.5 -- or -- The solution adjusted to 6.5 was stored. Thus, about the obtained sample, the content of an iodide, an amine (aromatic amine of isolation), and calcium disodium edetate was examined.

緩衝系 p H = 7.5	ヨウ化物 [μ g/ml]	アミン [重量%]	エデト酸 ナトリウム カルシウム [μ g/ml]
トロメタモール	11.8	0.062	90.8
トロメタモール/ グリシン	8.2	0.058	92.7
トロメタモール/ コハク酸	2.6	0.048	93.7
トロメタモール/ H E P E S	6.6	0.070	94.2

緩衝系 p H = 6.5	ヨウ化物 [μ g/ml]	アミン [重量%]	エデト酸 ナトリウム カルシウム [μ g/ml]
トロメタモール	8.6	0.014	89.9
トロメタモール/ グリシン	7.1	0.015	89.0
トロメタモール/ コハク酸	1.4	0.024	93.7
トロメタモール/ H E P E S	7.1	0.014	90.9

the stability of an X-ray-contrast-medium solution -- pH \leq 6.5 fatty tuna pure in a field -- already having been improved with the meta-mall buffer solution was shown. However, when the buffer solution of invention was used, it was able to stabilize in the still larger range. this data -- especially -- fatty tuna -- it accepts to the combination of a meta-mall and a succinic acid.

Example 10: Buffer capacity of the various buffer solutions The buffer capacity of the various buffer solutions is illustrated by drawing 4 .

Example 11: Stability of the placebo liposome which used the buffer solution The placebo liposome solution which consists of soybean phosphatidylcholine (150 mg/ml) It manufactures using continuous system high voltage extrusion (five paths 0.8/0.6/0.4 and a 0.2-micrometer polycarbonate millipore filter plate activity) on the basis of an activity of various buffer systems (it adjusts to pH 6.5). Only the time amount mentioned to the table within the closed cylinder for injection of 10 ml carried out autoclave processing of the aliquot of this suspension (121 degrees C). Thus, about the obtained sample, grain size (photon correlation spectroscopy) and the content of lysophosphatidylcholine were investigated (the HPLC method).

緩衝液	殺菌時間 〔分〕	平均直径 〔nm〕	L P C 含有量 〔mg/g〕
20 mM クエン酸／NaOH	0	161	1.7
	20	154	2.5
	60	161	3.3
20 mM リン酸塩緩衝液 (図 1 参照)	0	164	1.5
	20	165	2.0
	60	160	3.5
10 mM トリス／ 10 mM コハク酸	0	154	0.7
	20	157	0.9
	60	158	1.2
10 mM トリス／ 10 mM グリシン	0	159	0.6
	20	153	0.9
	60	154	1.3

[Translation done.]

* NOTICES *

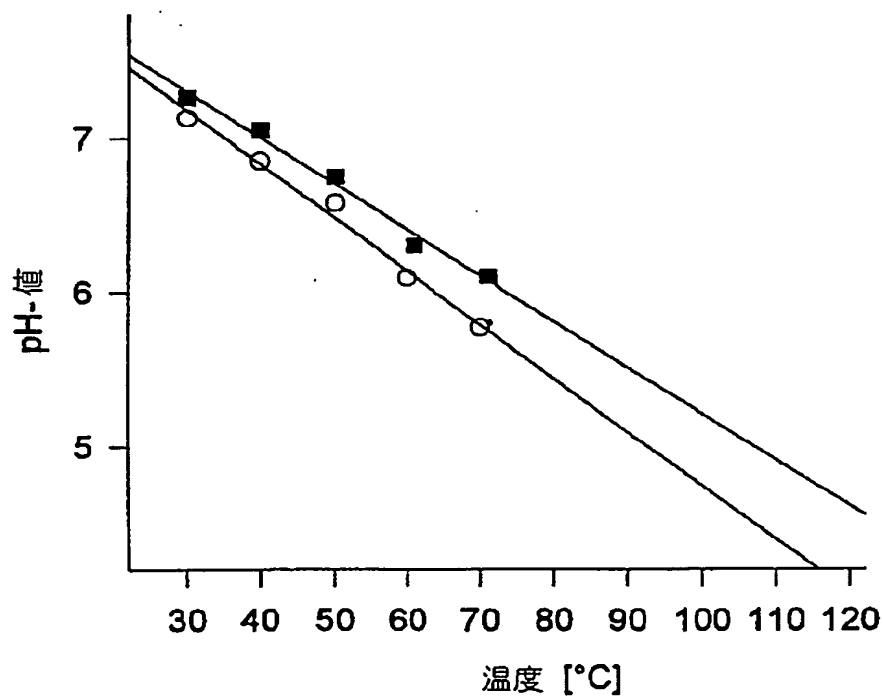
JPO and NCIPI are not responsible for any damages caused by the use of this translation.

1. This document has been translated by computer. So the translation may not reflect the original precisely.
2. **** shows the word which can not be translated.
3. In the drawings, any words are not translated.

DRAWINGS

[Drawing 1]

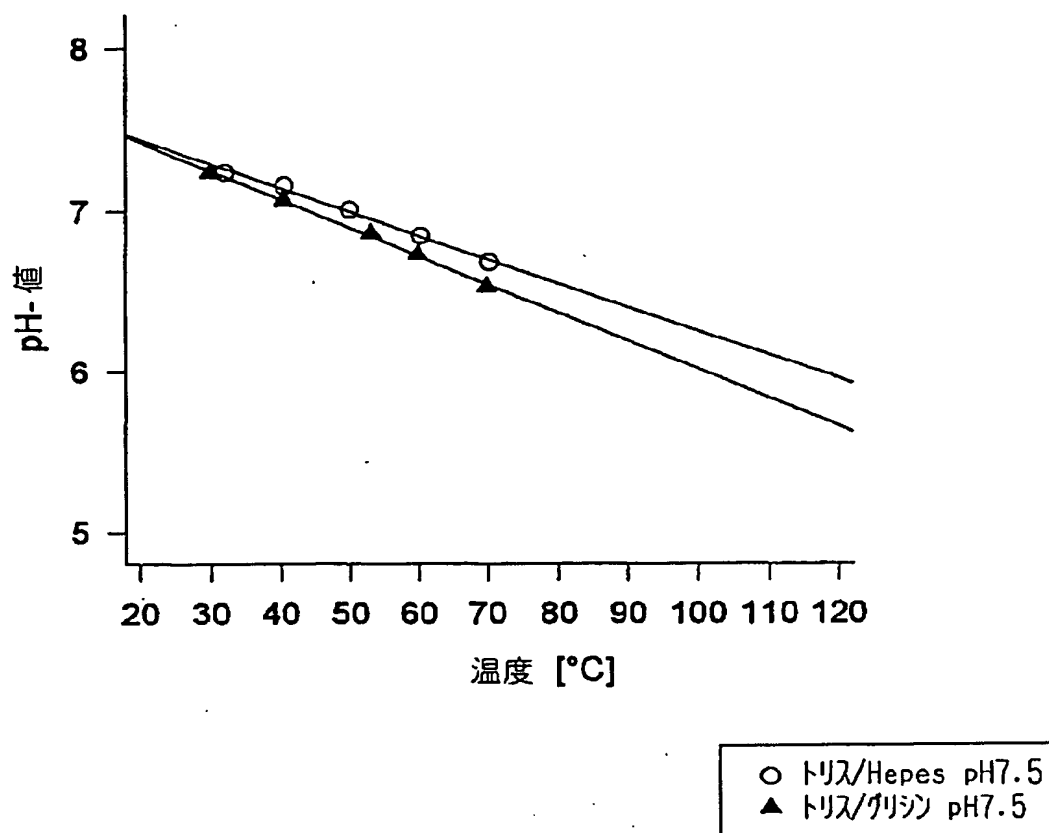
Figur 1 / 4:



○ 温度補償無しで測定
■ 温度補償有りで測定

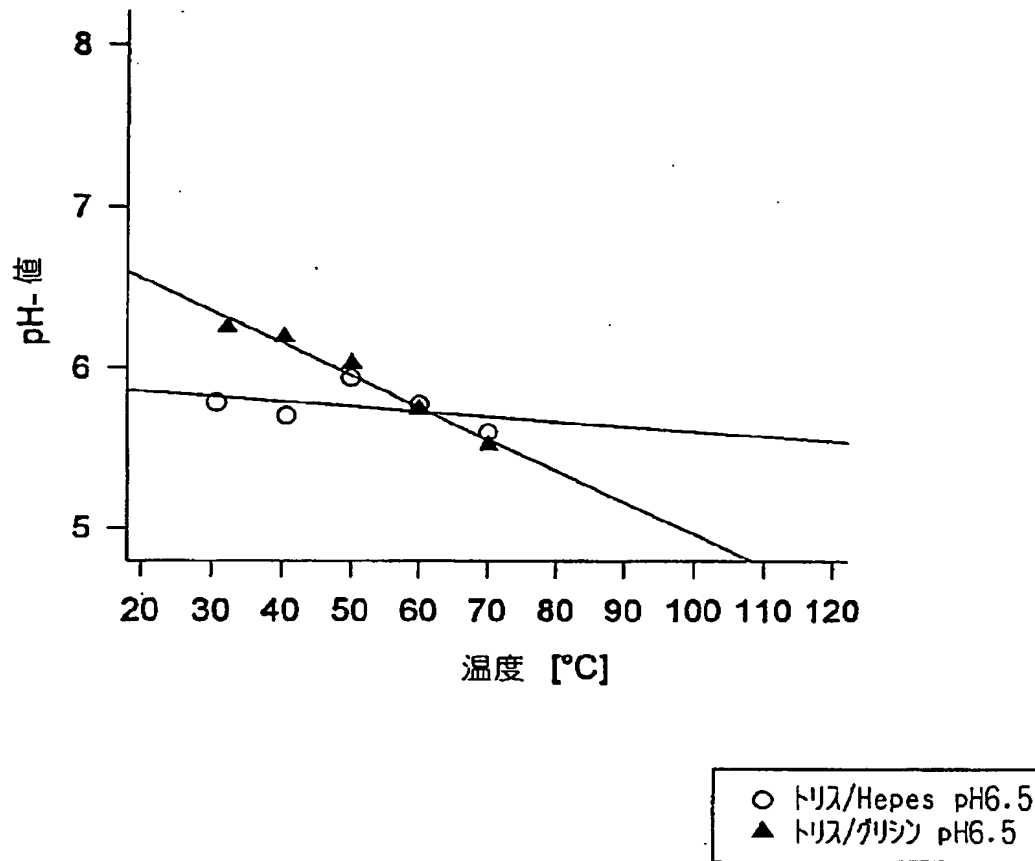
[Drawing 2]

Figur 2 / 4:



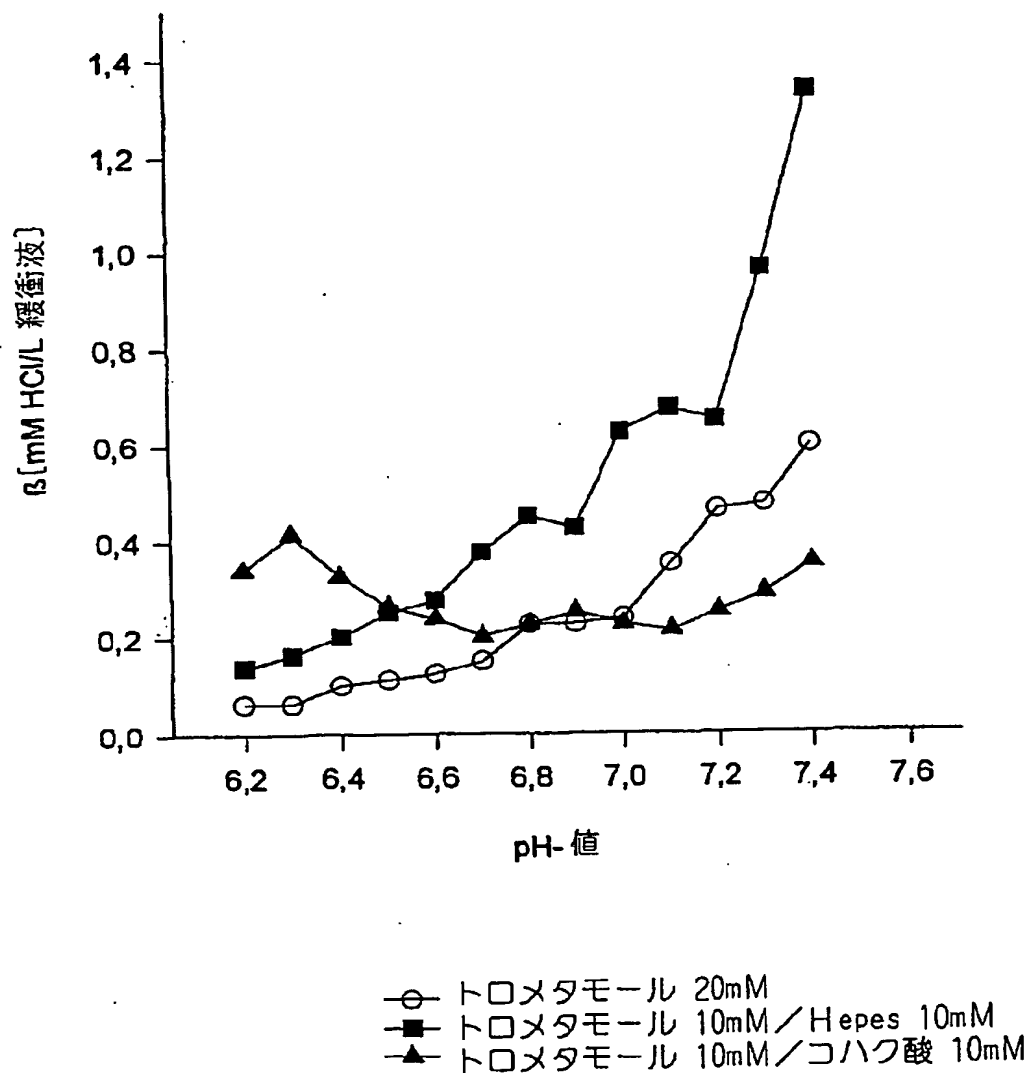
[Drawing 3]

Figur 3 / 4:



[Drawing 4]

Figur 4 / 4:



[Translation done.]

* NOTICES *

JPO and NCIPi are not responsible for any damages caused by the use of this translation.

1. This document has been translated by computer. So the translation may not reflect the original precisely.
2. **** shows the word which can not be translated.
3. In the drawings, any words are not translated.

CLAIMS

[Claim(s)]

1. The buffer solution characterized by containing organic acid which has amine and at least one physiological compatibility which have at least one physiological compatibility.
2. The buffer solution according to claim 1 characterized by containing 2-amino-2-(hydroxymethyl)-1 and 3-propanediol as amine component.
3. The buffer solution according to claim 1 characterized by containing N-methyl glucamine as amine component.
4. The buffer solution according to claim 1 characterized by containing carboxylic acid of monovalence or many **, hydroxycarboxylic acid, keto acid, sulfonic acid, or amino acid as acid component.
5. The buffer solution according to claim 1 characterized by containing benzoic acid, succinic acid, maleic acid, glycolic acid, citric acid, malic acid, lactic acid, alpha-ketoglutarate, 2-[4-(2-hydroxyethyl)-1-piperazino]-ethane sulfonic acid, glycine, aspartic acid, phenylalanine, lysine, or arginine as acid component.
6. The buffer solution according to claim 1 characterized by containing 2-amino-2-(hydroxymethyl)-1 and 3-propanediol and glycine.
7. The buffer solution according to claim 1 characterized by containing 2-amino-2-(hydroxymethyl)-1 and 3-propanediol and HEPES.
8. The buffer solution according to claim 1 characterized by containing 2-amino-2-(hydroxymethyl)-1 and 3-propanediol and succinic acid.
9. Activity of the buffer solution according to claim 1 for manufacturing drugs.
10. The activity of the buffer solution according to claim 1 for manufacturing an X-ray contrast medium, the contrast medium for MRT, a radiation diagnostic drug, or a radiation remedy.
11. The activity of the buffer solution according to claim 1 for manufacturing liposome suspension.
12. The activity of the buffer solution according to claim 1 for manufacturing the liposome suspension containing a contrast medium.

[Translation done.]

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.